

AMENDMENTS TO THE DRAWINGS

Figure 1 was amended to delete the brackets at the top of 1-1 and 1-2. Each of these amendments were made to increase the clarity of the figure, and to overcome the Examiner's objection to the same. No new matter has been added.

Applicants note that since the amendments to the Figures merely represented "changes in reference characters, designations of figures...", Annotated Sheets have not been provided in accordance with MPEP 608.02(v).

REMARKS**AMENDMENTS TO THE SPECIFICATION**

The legend of Figure 1 beginning on page 11, line 31, was amended to delete the phrase “labeled in red are classified as resistant, and those labeled in blue are”, to append the phrase “have been” before the “classified” term”; to append the term “being” prior to the sensitive term, to append the phrase “or resistant” prior to the “to BMS-A” phrase, to append the phrase “are identified in Table 1” after the “according to their IC₅₀” phrase, to delete the “and” after the phrase “The expression levels greater than the median are shaded in red,”, and to append the phrase “, while those at the mean are shaded in black” to overcome the Examiner’s objection to the same. Support for these amendments may be found in Figure 1 as originally submitted and in Table 1. No new matter has been added.

The legend of Figure 7 beginning on page 14, line 4 was amended to delete the “and” after the phrase “The expression levels greater than the median are shaded in red,”, and to append the phrase “, while those at the mean are shaded in black” to overcome the Examiner’s objection to the same.

STATUS OF THE CLAIMS:

Claims 1 to 40 and 42 to 52 are cancelled.

Claim 41 has been amended.

Claim 41 is pending.

Claim 41 was amended to substitute the phrase “at least one informative” with the phrase “the EphA2 gene in a sample,” to delete the phrase “, wherein said at least one informative gene is EphA2”, to append the phrase “and comparing the normalized value of said gene expression product to the normalized value of an internal control gene,” after the “the EphA2 gene in a sample,” phrase, to substitute the phrase “increased expression of said gene expression product in said sample relative to a standard” with the phrase “an expression level of said gene expression product in said sample that is at least three-fold higher relative to the expression level of said internal control”, and substituting the phrase “decreased expression of said gene expression product in said sample relative to a standard” with the phrase “an expression level of said gene expression product in said sample that is at least three-fold lower relative to the expression level of said internal control”. Support may be found in Claim 41 as previously submitted, on page 4 and 5, on page 7, in the legend of Figure 1 on page 12, in the legend of Figure 7 on page 14, in Example 1, in Example 2, in the specification as originally filed. Applicants note that “three-fold” change in absolute expression was used as a criterion for identifying sensitive and resistant predictor genes, and thus this threshold applies to determining whether a gene exhibited either increased or decreased expression relative to the internal control gene GAPDH. No new matter has been added.. Applicants assert that these amendments were not made to overcome any issues related to the patentability of this claim and that Applicants right to equivalents of Claim 41 is reserved. No new matter has been added.

Applicants remind the Examiner that there is no requirement for a limitation to be explicitly supported word-for-word in the specification in order for the written description requirement to be satisfied. Rather, the M.P.E.P. states that claim limitations may be supported in the specification through “express, implicit, or inherent disclosure...” and that “there is no *in haec verba* requirement” (see M.P.E.P. 2163(I)(B))(emphasis added). The M.P.E.P. teaches that whether the written description requirement is met turns on whether “...a skilled artisan would have understood the

inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification...See, e.g., Vas-Cath, 935 F.2d at 1563, 19 USPQ2d at 1116; Martin v. Johnson, 454 F.2d 746, 751, USPQ 391, 395 (CCPA 1972)(stating “the description need not be in *ipsis verbis* [i.e., “in the same words”] to be sufficient”). (see M.P.E.P. 2163(II)(A)(3)(a))(emphasis added).

I. Miscellaneous

a. Objections to the Drawings

The Examiner has objected to the drawings stating:

Figures 1 and 7 are objected to because neither the figures nor the legends thereto explain the meaning of the black squares in the figures.

Figure 1 is further objected to because the legend thereto states: "The cell lines labeled...in blue are classified as sensitive to BMS-A"; however, there is no blue color in Figure 1. Moreover, the title of the figure indicates that the data represent polynucleotide expression patterns, not sensitivity to BMS-A.

Figures 1 and 7 are objected to because the brackets at the top; linking cells, are not explained.

In response, Applicants have submitted Replacement Figures 1-1 and 1-2 which address and overcome the Examiner's objections to the drawings.

Re: reference to blue colored text in the legend of Figure 1, Applicants point out that Figure 1, as originally filed, contained both red and blue text above each column. However, the Replacement Sheet for Figure 1 as presented during prosecution of the instant application did not contain the colored text headings because the identity of both the sensitive and resistant cell lines were already provided in Table 1 of the specification. The Replacement Sheet(s) for Figure 1 submitted herewith are consonant with the previous Replacement Figures submitted and accordingly do not contain colored text headings. As a result, the legend of Figure 1 has been amended to delete reference to the colored text headings, and to refer to the sensitive/resistant cell line classifications provided in Table 1.

Re: the brackets above the cell lines listed in Figure 1, Applicants have amended Figure 1 to delete the bracketing.

Re: the black squares in Figures 1 and 7, these represent expression values that are at the mean. As noted in the legend of Figures 1 and 7, those cells showing expression above the mean are represented in green, whereas those cells showing expression below the mean are represented in red. Both legends of Figures 1 and 7 have been amended to denote the black representation.

II. Rejections under 35 U.S.C. § 101

a. The Examiner has withdrawn the rejection of Claim 41 under 35 U.S.C. § 101 alleging it is unpatentable over Claim 16 of US Application 11/072,175 under the judicially created

doctrine of obviousness-type double patenting, but reinstated the rejection over Claims 21 and 23 to 28 of US Application 11/072,175 on the same grounds. Specifically, the Examiner alleges:

Provisional rejection of Claim 41 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 16 of US Application 11/072,175, for the reasons set forth in the prior actions, is withdrawn because Claim 16 has been cancelled. However, Claim 41 is herein provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 21 and 23-28 of US Application 11/072,175, for the same reasons previously explained for Claim 16 therein.

Applicants respectfully disagree with the Examiner's allegation. However, Applicants note that the Examiner's rejection is "provisional", and in accordance with MPEP 804(I)(B), no action is currently required on behalf of Applicants.

III. Rejections under 35 U.S.C. § 112, Second Paragraph

a. The Examiner rejected Claim 41 under 35 U.S.C. § 112, second paragraph alleging that it is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner alleges that:

Claim 41 recites a method wherein identifying a breast cancer cell as being sensitive or resistant to a tyrosine kinase inhibitor is determined by comparing the expression of specific gene(s) "relative to a standard" (lines 5 and 7). However, neither the claims nor the specification define what said "standard" is. The metes and bounds of the recited invention are unclear.

Applicants respectfully disagree with the basis for the Examiner's rejection and assert the instant specification adequately describes the meaning of the "standard". According to the MPEP,

The fact that claim language, including terms of degree, may not be precise, does not automatically render the claim indefinite under 35 U.S.C. 112, second paragraph. *Seattle Box Co., v. Industrial Crating & Packing, Inc.*, 731 F.2d 818, 221 USPQ 568 (Fed. Cir. 1984). Acceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification.

(MPEP § 2173.05(b)). A skilled artisan, upon reading the teachings of the specification, would understand the meaning of what is meant by the "standard" term and thus would equate it to be consonant with a "reference". However, in the sole interest of facilitating prosecution, Applicants have amended Claim 41 to append the phrase "comparing the normalized value of said gene

expression product to the normalized value of an internal control gene,” prior to the first wherein term, substituting the phrase “increased expression of said gene expression product in said sample relative to a standard” with the phrase “an expression level of said gene expression product in said sample that is at least three-fold higher relative to the expression level of said internal control”, and substituting the phrase “decreased expression of said gene expression product in said sample relative to a standard” with the phrase “an expression level of said gene expression product in said sample that is at least three-fold lower relative to the expression level of said internal control”.

Accordingly, Applicants believe the Examiner’s rejection of Claim 41 under 35 U.S.C. § 112, second paragraph has been overcome in consideration of these amendments.

b. The Examiner rejected Claim 41 under 35 U.S.C. § 112, second paragraph alleging that it is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner alleges that:

Claim 41 recites the phrase "determining the expression profile of a gene expression product from at least one informative gene in a sample, wherein said at least one informative gene is EphA2". It is unclear from said phrase whether the method encompasses (i) determining the expression profile of only the EphA2 gene and from the expression profile of EphA2 gene products, predicting sensitivity/resistance to the inhibitor or (i) determining the expression profile of a population of genes, wherein EphA2 is one gene of the population, and from the expression profile of said population of genes, predicting sensitivity/resistance to the inhibitor. The skilled artisan would not know the metes and bounds of the invention. For purposes of examination, it is assumed that said phrase means determining the expression profile of a population of genes, wherein EphA2 is one gene of the population, and from the expression profile of said population of genes, predicting sensitivity/resistance to the inhibitor.

Applicants disagree with the Examiner’s rejection. However, in the sole interest of facilitating prosecution, Applicants have amended Claim 41 to substitute the phrase “at least one informative” with the phrase “the EphA2”, and deleting the phrase “, wherein said at least one informative gene is EphA2”. Accordingly, Applicants believe the Examiner’s rejection of Claim 41 under 35 U.S.C. § 112, second paragraph has been overcome.

IV. Rejections under 35 U.S.C. § 112, first paragraph

The Examiner has maintained the rejection of Claim 41 under 35 U.S.C. § 112, first paragraph. Specifically, the Examiner alleges that:

Rejection of Claim 41 under 35 U.S.C. 112, first paragraph/lack of enablement, for the reasons explained in the prior action, is maintained.

The specification is enabling for determining the sensitivity (IC₅₀) of a panel of 23 breast cancer cell lines to BSM-A, calculating the log₁₀IC₅₀ for each cell line, calculating the mean log₁₀IC₅₀ for the panel of cell lines, and, based on said mean, arbitrarily dividing said panel of cell lines into sensitive (below the mean) and resistant (above the mean). The specification also is enabling for using hybridization methods to assess the relative expression of EphA2-encoding mRNA in said panel of breast cancer cell lines (para bridging pg 105-106), calculating the median expression of EphA2-encoding mRNA for said 23 cell lines, and, based on said median, arbitrarily dividing said panel of cell lines into those having expression greater than the median and those having expression less than the median (Fig. 1). Using the above arbitrary division of said panel of 23 breast cancer cell lines, the specification is enabling for analyzing for a correlation between expression levels of EphA2-encoding mRNA and sensitivity/resistance to BSM-A for (Fig 1, gene 1, vs Table I). Assuming the black squares on the right (red) side of Fig 1 represents high expression, the number of cell lines in which sensitivity to BSM-A correlates with EphA2 expression is 17/23 = 74% (none of the BT549, HCC38, MDA-MB-468, MDA-MB-436, or MDA-MB-435 cell lines showed such a correlation). However, the specification does not reasonably provide enablement for any method of predicting whether any breast cancer cell will be sensitive or resistant to any protein tyrosine kinase inhibitor that directly or indirectly inhibits the activity of Src, Fgr, Fyn, Yes, Blk, Hck, Lck, Lyn, BCR-ABL, PDGFR, c-Kit, and EphA2, by assaying the levels of any population of gene products, wherein the population comprises EphA2.

The specific reagents and steps used for any method determine the method's success. Predictability of which steps and reagents can be used to obtain the desired effect requires a knowledge of, and guidance with regard to how said steps and reagents relate to the desired outcome. In the instant case, the skilled artisan must be provided guidance as to how any population of gene products comprising EphA2 can be used to predict the sensitivity/resistance of any breast cancer cell to essentially any protein tyrosine kinase inhibitor. However, this case is limited to correlating the expression of EphA2 to sensitivity/resistance to BSM-A in a single panel of 23 breast cancer cell lines.

Methods for analyzing expression of gene products as well as testing sensitivity to protein kinase inhibitors are known in the art. However as recently as 2007, the use of gene product expression profiling for predicting the responsiveness of breast cancer cells to any specific compound was unpredictable (Gruvberger-Saal et al, 2006, pg 1021-1023; Sotiriou et al, 2007, pg 550-551). The specification fails to provide evidence as to which of the essentially unlimited number of panels of gene products comprising EphA2 can be used to successfully predict the sensitivity of any breast cancer cell line to any protein kinase inhibitor. In fact, Applicants' 'declaration of September 2006 provides evidence that analysis of genes, in addition to EphA2, reduces the predictability of the recited method (Exhibits G-K). In the absence of guidance as to which populations of genes to use, the skilled artisan is reduced to the undue burden of analyzing the expression of any population of gene products, testing the sensitivity to any protein kinase inhibitor, and determining which genes can be used to predict sensitivity/resistance to any said kinase inhibitor. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification.

The specification does not support the broad scope of Claim 41 which, encompasses all methods of predicting whether any breast cancer cell will be sensitive or resistant to any protein tyrosine kinase inhibitor that directly or indirectly inhibits the activity of Src, Fgr, Fyn, Yes, Blk, Hck, Lck, Lyn, BCR-ABL, PDGFR, c-Kit, and EphA2, by assaying the levels of any population of gene products, wherein the population comprises EphA2. The specification does not support the broad scope of

Claim 41 because the specification does not establish: (A) a standard by which to compare whether the EphA2 gene product, or any other specific gene product, is "increased" or "decreased" in any specific breast cancer cell; (B) a standard by which to determine whether a specific breast cancer cell is sensitive or resistant to any specific protein tyrosine kinase inhibitor; (C) a correlation between expression of EphA2-encoding mRNA and sensitivity to BMS-A in any population of breast cancer cells other than the one population disclosed in the specification; (D) a correlation between expression of any EphA2 polypeptide to be assayed, or any other polypeptide, and sensitivity to any encompassed tyrosine kinase inhibitor; (E) a correlation between expression of any possible encompassed gene product to be assayed and sensitivity to any encompassed tyrosine kinase inhibitor; (F) the specification provides insufficient guidance as to which of the essentially infinite possible choices of populations of gene products can be successfully analyzed to predict the sensitivity/resistance to the essentially infinite possible choices of protein tyrosine kinase inhibitors in any breast cancer cell.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of methods to predict whether any breast cancer cell will be sensitive or resistant to any protein tyrosine kinase inhibitor that directly or indirectly inhibits the activity of Src, Fgr, Fyn, Yes, Btk, Hck, Lck, Lyn, BCR-ABL, PDGFR, c-Kit, and EphA2, by assaying the levels of any population of gene products, wherein the population comprises EphA2. Without sufficient guidance, determination of the identity of methods having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988).

Applicants disagree with the Examiner's maintenance of the rejection of Claim 41 under 35 U.S.C. § 112, first paragraph, and assert that the claimed invention is enabled based solely upon the teachings of the instant specification. Applicants point out that corroborating data (e.g., see the Dr. Huang Declaration submitted on September 14, 2006), and arguments in favor of the claimed invention being enabled, have already been previously set out in the record and need not be repeated.

Nonetheless, in the sole interest of facilitating prosecution, Applicants have amended Claim 41 to substitute the phrase "at least one informative" with the phrase append the phrase "the EphA2", to delete the phrase "wherein said at least one informative gene is EphA2", to append the phrase "and comparing the normalized value of said gene expression product to the normalized value of an internal control gene," after the after the "the EphA2 gene in a sample, " phrase, to substitute the phrase "increased expression of said gene expression product in said sample relative to a standard" with the phrase "an expression level of said gene expression product in said sample that is at least three-fold higher relative to the expression level of said internal control", and substituting the phrase "decreased expression of said gene expression product in said sample relative to a standard" with the phrase "an expression level of said gene expression product in said sample that is at least three-fold lower relative to the expression level of said internal control". Accordingly, Applicants believe the

Examiner's rejection of Claim 41 under 35 U.S.C. § 112, first paragraph has been overcome in consideration of these amendments and respectfully request that the rejection be withdrawn. Applicants believe the Examiner's comments in sections (B), (C), (F), and (H) in the February 12, 2008 Action on pages 9 to 11 have also been overcome in consideration of these amendments and respectfully request that the rejection be withdrawn.

Regarding the Examiner's comments in sections (D), (E), and (G), Applicants again assert that maintaining the rejection of Claim 41 on these grounds is improper on the basis the Examiner has failed to meet her burden in establishing that one skilled in the art would not know how to make and use the invention embraced by these claims without undue experimentation. Applicants point out that the "test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." (MPEP 2164.01). In establishing a reasonable basis for rejecting a claim for lack of enablement, the Examiner must make "specific findings of fact, supported by the evidence, and then draw[] conclusions based on these findings of fact" (MPEP 2164.04) - the "examiner should never make the determination based on personal opinion." (MPEP 2164.05).

Applicants reassert that the test for enablement is whether the claimed invention is described in such a way as to enable any person skilled in the art "to make or use the invention from the disclosures in the patent coupled with information in the art without undue experimentation". See *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). In addition, the MPEP states the fact that "experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation". MPEP 2164.01; *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom.*, *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985).

In support of maintaining the rejection of Claim 41 under 35 U.S.C. § 112, first paragraph, the Examiner alleges "the genus of inhibitors that affect, either directly or indirectly, the activity of Src, Fgr, Fyn, Yes, Blk, Hck, Lck, Lyn, BCR-ABL, PDGFR, c-Kit, and EphA2 is a large genus of inhibitors". However, the Examiner has failed to actually establish that the genus is in fact so large that undue experimentation would be required. It is Applicant's understanding that very few compounds, aside from BMS-A, -B, -C, -D, and -E, actually inhibit Src, Fgr, Fyn, Yes, Blk, Hck, Lck, Lyn, BCR-ABL,

PDGFR, c-Kit, and EphA2. Accordingly, Applicants believe the Examiner's rejection of Claim 41 under 35 U.S.C. § 112, first paragraph is improper and should be withdrawn.

III. Rejections under 35 U.S.C. § 112 – First Paragraph

a. The Examiner has maintained the rejection of Claim 41 under 35 U.S.C. § 112, first paragraph alleging:

Rejection of Claim 41 under 35 U.S.C. 112, first paragraph/written description, for the reasons explained in the prior action, is maintained.

These arguments are not found to be persuasive for the following reasons. It is acknowledged that Applicants were in possession of a method whereby analysis of EphA2 expression levels in a single population of breast cancer cells to correlate sensitivity of the cells to BMS-A and specific variants thereof. However, said example does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of a method for predicting whether any breast cancer cell will be sensitive or resistant to any protein tyrosine kinase inhibitor that directly or indirectly inhibits the activity of Src, Fgr, Fyn, Yes, Blk, Hck, Lck, Lyn, BCR-ABL, PDGFR, c-Kit, and EphA2, by assaying the levels of any population of gene products, wherein the population comprises EphA2. Given this lack of description of representative species encompassed by the genera of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Applicants disagree with the Examiner's maintenance of the rejection of Claim 41 under 35 U.S.C. § 112, first paragraph, and assert that the claimed invention provides sufficient description to establish that Applicants were in possession of the claimed invention as outlined elsewhere in the record and corroborated by the Dr. Huang Declaration. Nonetheless, in the sole interest of facilitating prosecution, Applicants have amended Claim 41 to substitute the phrase “at least one informative” with the phrase append the phrase “the EphA2 ”, to delete the phrase “, wherein said at least one informative gene is EphA2”, to append the phrase “and comparing the normalized value of said gene expression product to the normalized value of an internal control gene,” after the after the “the EphA2 gene in a sample, ” phrase, to substitute the phrase “increased expression of said gene expression product in said sample relative to a standard” with the phrase “an expression level of said gene expression product in said sample that is at least three-fold higher relative to the expression level of said internal control”, and substituting the phrase “decreased expression of said gene expression product in said sample relative to a standard” with the phrase “an expression level of said gene expression product in said sample that is at least three-fold lower relative to the expression level of said internal control”. Accordingly, Applicants believe the Examiner's rejection of Claim 41

under 35 U.S.C. § 112, first paragraph has been overcome in consideration of these amendments and respectfully request that the rejection be withdrawn.

b. The Examiner has maintained the rejection of Claim 41 under 35 U.S.C. § 112, first paragraph alleging:

Claim 41 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the Inventors, at the time the application was filed, had possession of the claimed invention. Claim 41 introduces the limitation of comparing the expression of a gene product "relative to a standard". The specification fails to describe said limitation and, thus, Claim 41 is rejected under 35 U.S.C. 112, first paragraph, for introducing New Matter.

Applicants respectfully disagree with the basis for the Examiner's rejection and assert the instant specification adequately describes the meaning of the "standard". According to the MPEP,

The fact that claim language, including terms of degree, may not be precise, does not automatically render the claim indefinite under 35 U.S.C. 112, second paragraph. *Seattle Box Co., v. Industrial Crating & Packing, Inc.*, 731 F.2d 818, 221 USPQ 568 (Fed. Cir. 1984). Acceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification.

(MPEP § 2173.05(b)). A skilled artisan, upon reading the teachings of the specification, would understand the meaning of what is meant by the "standard" term and thus would equate it to be consonant with a "reference". However, in the sole interest of facilitating prosecution, Applicants have amended Claim 41 to append the phrase "comparing the normalized value of said gene expression product to the normalized value of an internal control gene," prior to the first wherein term, substituting the phrase "increased expression of said gene expression product in said sample relative to a standard" with the phrase "an expression level of said gene expression product in said sample that is at least three-fold higher relative to the expression level of said internal control", and substituting the phrase "decreased expression of said gene expression product in said sample relative to a standard" with the phrase "an expression level of said gene expression product in said sample that is at least three-fold lower relative to the expression level of said internal control".

Accordingly, Applicants believe the Examiner's rejection of Claim 41 under 35 U.S.C. § 112, first paragraph has been overcome in consideration of these amendments.


Applicants believe that all of the Examiner's rejections and objections have been overcome and that all of the pending claims before the Examiner are in condition for allowance. An early Office Action to that effect is, therefore, earnestly solicited.

A one-month extension is hereby requested pursuant to 37 CFR §1.136(a). Please charge Deposit Account No. 19-3880 in the name of Bristol-Myers Squibb Company in the amount of \$120 for payment of the extension fee.

If any fee is due in connection herewith not already accounted for, please charge such fee to Deposit Account No. 19-3880 of the undersigned. Furthermore, if any extension of time not already accounted for is required, such extension is hereby petitioned for, and it is requested that any fee due for said extension be charged to the above-stated Deposit Account.

Respectfully submitted,

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